

# Surgical treatment of pulmonary hypertension in protein C deficiency

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## Abstract

**Two patients with protein C deficiency developed symptomatic pulmonary hypertension secondary to chronic pulmonary embolism. They were successfully treated by thromboendarterectomy.**

The protein C system is a natural profibrinolytic system consisting of protein C and protein S, which are vitamin K dependent plasma proteins, and thrombomodulin a surface protein of endothelial cells. Together they set off a cascade that produces protein C. This inactivates factors V and VIII and neutralises the inhibitor of tissue type plasminogen activator.<sup>1</sup> There is an autosomal dominant form protein C deficiency<sup>2</sup> that has variable expressivity.<sup>3</sup> Affected patients have a history of venous thromboembolism with superficial thrombophlebitis. The homozygous

condition is normally fatal in early life, causing neonatal purpura fulminans,<sup>4</sup> although this has recently been treated successfully by orthotopic liver transplantation.<sup>5</sup> Treatments used to correct the coagulation disorder in the heterozygous condition include heparin, fresh frozen plasma, danazol,<sup>6</sup> protein C extract, and coumarin anticoagulants. Anticoagulants, however, have been implicated in cases of skin necrosis in the presence of protein C deficiency.<sup>7</sup>

We have recently successfully treated secondary pulmonary hypertension which developed in two patients with this condition.

## Case reports

### PATIENT 1

A woman was referred to us at age 29 with a history of deep vein thromboses and pulmonary emboli causing dyspnoea at rest. Her protein C activity was 35 U/dl (normal range 70-140 U/dl) and protein C ag 48 U/dl (normal range 70-140 U/dl). Her father was also diagnosed as having protein C deficiency.

A ventilation/perfusion (V/Q) scan showed lack of perfusion of the left lung (fig 1) and a pulmonary angiogram showed that the left pulmonary artery was occluded and that there were segmental filling defects in the contralateral lung. At rest her pulmonary artery pressure was 45/20 mm Hg rising to 70/25 mm Hg on exercise and her oxygen saturation was 75% at rest falling to 50% on exercise.

At operation full cardiopulmonary bypass was used to cool the patient to 20°C. The aorta was cross clamped and the heart was arrested by crystalloid cardioplegia and topical cooling. The extracorporeal circulation was arrested for 20 minutes to control torrential collateral back bleeding (of bronchial origin) and a thromboendarterectomy was performed through a longitudinal pulmonary arteriotomy. The endarterectomy was started in the main pulmonary artery, which was coated with a thin layer of fibrinous material, and extended out to extract solid cores from the segmental branches. After operation she was treated with intravenous heparin followed by full course of warfarin.

A postoperative V/Q scan showed a considerable improvement in the perfusion of the left lung (fig 2). The patient was allowed home eight days postoperatively and when seen six weeks later was in New York Heart Association (NYHA) class I.

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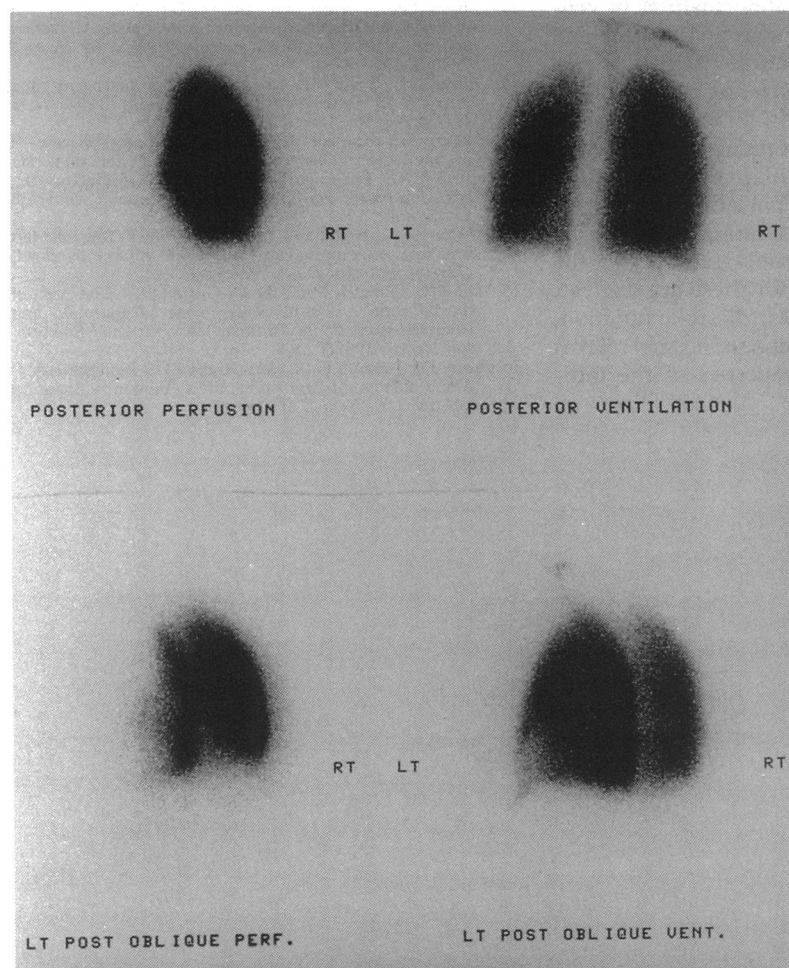


Figure 1 Preoperative V/Q scan in patient 1.

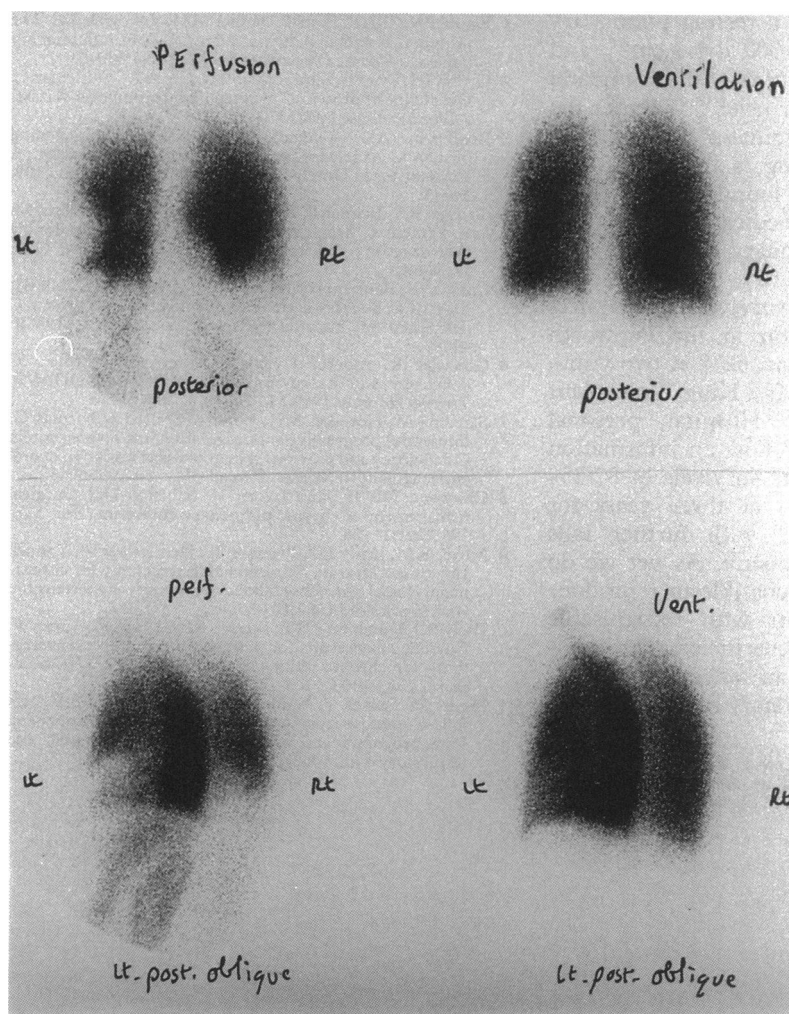


Figure 2 Postoperative V/Q scan in patient 1.

#### PATIENT 2

A 39 year old man with asthma who complained of worsening of dyspnoea was found to have a cardiac murmur. A chest radiograph showed an oligemic right lung and a prominent left pulmonary artery.

Digital subtraction angiography showed an occlusion of the right pulmonary artery and "pruning" of branches of the left (fig 3). At right heart catheterisation the pulmonary

artery pressure was 80/30 mm Hg and the oxygen saturation was 85%.

A venogram showed the right femoral vein hardly filled at all. A clotting survey showed protein C antigen concentration of 21 U/dl and protein C activity of 34 U/dl. All surviving immediate relatives were screened and found to have normal values. The patient was referred for operation.

A pulmonary thromboendarterectomy was carried out as for the last patient. Again the occlusion process extended from the main pulmonary artery to the peripheral vessels. After operation he was fully anticoagulated with heparin initially and then with warfarin. His pulmonary artery pressure was 30/15 mm Hg, and a repeat angiogram performed 10 days postoperatively showed normal perfusion on both sides (fig 4).

He was discharged 18 days after operation and when seen two months and 10 months later was in NYHA class I. A further pulmonary digital subtraction angiogram at 12 months showed full revascularisation of both lungs.

#### Discussion

Pulmonary emboli normally resolve by active fibrinolysis. Studies using pulmonary scanning and arteriography showed complete dissolution 8–4 days after the event. A proportion (22%) of patients continued to have signs of the disease and between 0.5 and 4% went on to develop pulmonary hypertension.<sup>8</sup> Whether this was due to further silent emboli or changes in the unobstructed vasculature was unclear.<sup>9</sup> In one study, retrospective examination of data showed that two thirds of the patients had had one major event rather than repetitive emboli.<sup>9</sup> Whatever the cause it is likely that patients with a defect of fibrinolysis such as protein C deficiency are more likely to develop secondary pulmonary hypertension. These patients are usually treated with anticoagulation, fibrinolysis, and diuretics—with vasodilators if cor pulmonale develops. The surgical options are a heart-lung transplantation or pulmonary thromboendarterectomy. The criteria for pulmonary thromboendarterectomy include dysp-

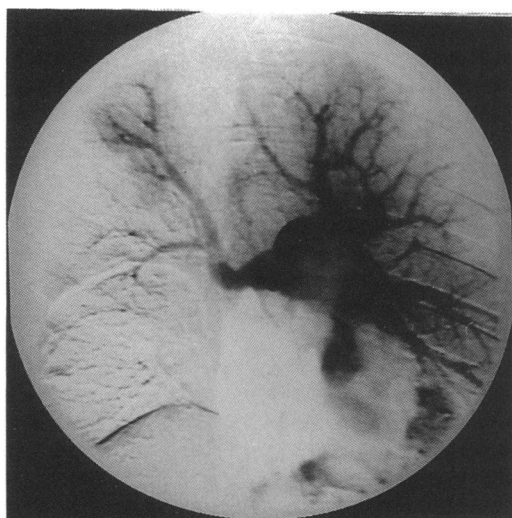


Figure 3 Preoperative pulmonary angiogram in patient 2.

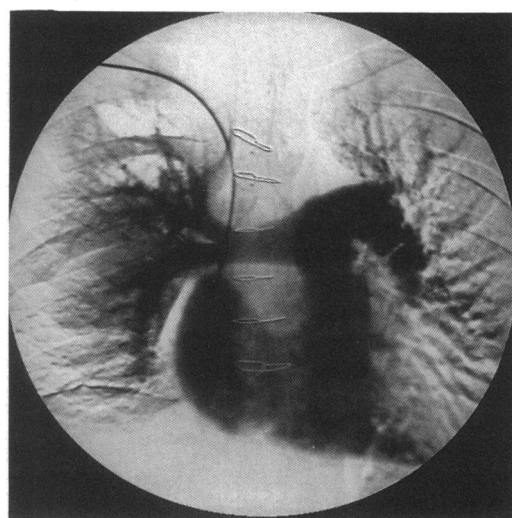


Figure 4 Postoperative pulmonary angiogram in patient 2.

noea (NYHA class IV), a resting pulmonary vascular resistance of  $\geq 300$  dyn.s.cm<sup>-5</sup>, and obstruction occurring at least at the segmental or preferably at the lobar level.<sup>10</sup> Whether the patient should be anticoagulated before operation, and if so for how long, is debatable.

In 1982 Riedel *et al* found that five year survival in patients on medical treatment was 30% if the mean pulmonary artery pressure was  $>30$  mm Hg and 10% if it was  $>50$  mm Hg.<sup>11</sup> The current survival figures after heart-lung transplantation in the Papworth series are 77% at one year, 62% at two years, and 59% at three years (Ms S King, Transplant Co-ordinator, Papworth Hospital, personal communication). Early follow up information from Daily *et al* suggests survivals of 87.3% at one year and 85.3% at three years for thromboendarterectomy<sup>10</sup> with further falls in pulmonary artery pressure. As yet we do not know whether it is possible to reproduce these figures in patients with recognisable defects of fibrinolysis; nevertheless, thromboendarterectomy remains an effective way of treating secondary pulmonary hypertension.

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